British Pharmacopoeia

Public consultation response: Guidance on the application of vector copy number quantification for the ATMP community

Introduction

The BP wishes to thank all stakeholders for contributing views on the Guidance on the application of vector copy number for the cell and gene therapy community. The continued cooperation and participation of our stakeholders ensures that our Advanced Therapy Medicinal Products (ATMP) work supports the needs of relevant users, and high-quality best practice guidance for ATMP analysis is produced in the interest of protecting public health.

The Agency is committed to ensuring the quality of medicines through its activities in the development of public quality standards that help to assure the safety and efficacy of medicines. The BP ATMP work is aligned to the Agency's Strategy for pharmacopoeial public quality standards for biological medicines[1] and the UK Government Life Sciences Vision[2].

This response document contains:

1. Report summary
2. Key themes from the responses
3. Outcomes
4. Implementation

1. Report summary

Between the 22nd July 2021 to 27th September 2021, the British Pharmacopoeia (BP) sought consultation on draft guidance on the application of vector copy number for the cell and gene therapy community. The guidance takes into account the fact that vector copy number quantification may be deployed in a range of scientific settings or environments. It recognises that the regulatory status in which the assay will be operated may influence the assay configuration and workflow. The guidance document attempts to cover assays being operated in the following environments:

- An academic research setting.
- An ATMP development programme (including GMP manufacture).
  - Within the sponsors own facilities.
  - Within outsourced contract vendors (e.g. CROs & CMOs).
- Clinical settings such as pathology laboratories for the analysis of patient samples.
- Clinical trials setting.
- Pre-clinical.

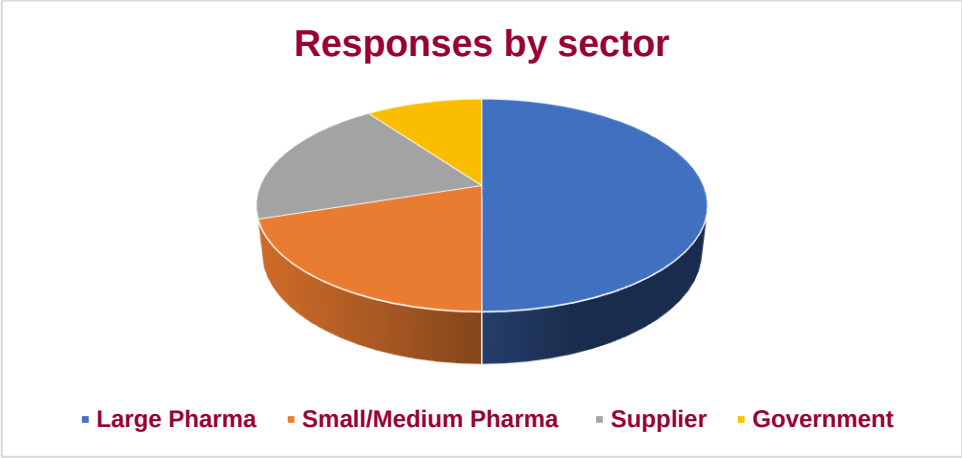
[1] https://www.gov.uk/government/consultations/strategy-for-pharmacopoeial-public-quality-standards-for-biological-medicines

[2] https://www.gov.uk/government/publications/life-sciences-vision/life-sciences-vision-html

There were eight responses received for the consultation, from a range of international organisations. These included small/medium and large pharmaceutical companies, suppliers, and cell and gene therapy groups. This diverse representation, as well as the expert familiarity of many of the respondents with vector copy number, indicates good feedback from the consultation. The extent of practical experience and wealth of knowledge from responders was evident from the detailed and balanced responses to the consultation.

2. Key themes from the responses

2.1 Response overview



The BP would like to make readers aware that although there were no responses from NHS to the public consultation, the WP ATMP and vector copy number subgroup that drafted the guidance document includes NHS representatives.

2.2 Benefits identified by responders

The guidance provides a valuable general overview and background for the development of PCR based methods for the reliable determination of VCN for AAV, thought to be particularly helpful for those new to development of VCN methods.

The guidance is concise, logically structured, and well-organized. The focus is on AAV vector copy number analysis and qPCR assay development and qualification best practices, although considerations of vector copy number analysis for LV products using dPCR id covered and appropriately draw from earlier sections, with the key differences highlighted.

The guidance covers the key technical aspects required for commercial-ready PCR-based analytical methods, regardless of the analyte or reportable. Existing guidelines are

consolidated in Tables 1 and 2, which provide an excellent resource for PCR-based ATMP analytical method developers.

Method changes or platform improvements are recognised as a potential risk and the guidance on managing this change during development is provided.

2.3 Potential challenges and improvements identified by responders

The guidance focusses on the qPCR reaction but gives limited information about the sample preparation and extraction of RNA/DNA. The sample preparation and replicate strategy are known causes of inconsistent results.

Information in the guidance is focussed on early-phase assays. Challenges in VCN development and implementation at early and late phase of product development are very different. This is especially critical during process changes or comparability. The critical assay control parameters, gaps, and mitigation solutions would be helpful to the reader.

The document in its current format does not consider measurement uncertainty when reporting quantitative VCN values.

The guidance covers VCN quantification based on quantification of a selected nucleic acid target within the viral vector using qPCR/dPCR. However, this guidance does not cover target selection in relation to partially/incompletely filled capsids. Using a single NA target sequence may lead to an inaccurate determination of “complete” vectors and consideration should be given to use of multiple target sequences when assessing products.

The guidance does not cover avoidance of contamination when using high copy number plasmid materials, which can impact accuracy of VCN quantification. Multiple types of negative controls are needed to control for such contamination.

Validation protocols and reports for VCN for AAV as well as LVV/RV would be useful.

2.4 Usefulness

The guidance will be useful to developers using AAV vectors, it provides standardized guidance for vector copy number assay development and validation. The guidance could be used as a reference for internal quality standard setting in developing PCR-based methods to measure vector copy numbers for autologous ex vivo and viral vector (AAV and lentiviral) based ATMPs.

The focus of the guidance is on VCN quantification using qPCR and dPCR based techniques and is based on existing qPCR/dPCR standards and guidance such as the MIQE guidelines and ISO 20395 which have be tailored to the specific requirements of VCN quantification. As such, this document will be a useful addition.

3. Review and approval process

Guidance valued

All comments have been considered by the BP Comission as well as the Working Party for ATMPs. Amendments have been made, as necessary. The document has also been reviewed by MHRA Licensing, Clinical Trials Unit, and Inspectorate divisions. The Working Party ATMP group is comprised of experts from a range of backgrounds including industry, academia, and NHS.

Technical amendments

The Working Party ATMP decided whether to make an amendment to the guidance based on group experience and knowledge, as well as prior agreements in relation to the scope of the document. Decisions around technical comments were made against regulatory expectations. Cross references to international regulations and guidance materials have been made intentionally due to the anticipated global usage of the guidance.

Non mandatory

The document is intended to be non-mandatory, best practice guidance. It does not constitute a prerequisite for licensing approval. All products need to be considered on a case-by-case basis and this document should be combined with product knowledge to aid decision making. The document is not necessarily exhaustive of expectations. It is the user's responsibility to ensure the appropriate methods are employed for their specific product, assay, and validation plan.

Clarity and style

Where language discrepancies, clarity and conciseness issues have been highlighted by consultation responders, amendments have been made. Users are assumed to have priorknowledge of the topic area of the guidance.

Scope

A number of new paragraphs and sections have been added to the document in response to stakeholder request, these include but are not limited to: requalification of the instrument, sample knowledge, set up, gating strategy, and data acquisition.

4. Implementation

In general, responses were supportive of the vector copy number guidance. Amendments have been made as a result of the consultation comments to the final document, which will be published on the BP Online product during the BP 2022 edition subject to the approval of the BP Commission.

The BP will continue to listen to our stakeholders as this guidance is published to ensure that the information is relevant and that any additional support our users may need is available. Please get in touch with us by email, BiolStandards@mhra.gov.uk, if you think we can provide further advice or support.